

EXHIBIT A152

ORIGINAL ARTICLE

A cohort mortality and nested case-control study of French and Austrian talc workers

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Objectives: To study whether the mortality from non-malignant and malignant respiratory diseases of workers employed in French and Austrian talc mines and mills is related to their long term occupational exposure.

Methods: Two historical cohorts were set up comprising all male subjects who had been working continuously for at least 1 year in a series of talc producing companies in France and Austria. The French cohort consisted of those employed at a site in the French Pyrenees and working between 1 January 1945 and 31 December 1994. The Austrian cohort consisted of the workers employed between 1 January 1972 and 31 December 1995 in one of four industrial sites in the Austrian Alps. The mortality within the cohorts was compared with local death rates. Two nested case-control studies focusing on non-malignant and malignant respiratory diseases were set up to estimate possible dose-response relations with cumulative exposure to talc dust based on an industry specific job exposure matrix.

Results: Mortality from lung cancer was in small excess in both cohorts (France, standardised mortality ratio (SMR) 1.23, 21 cases observed, 95% confidence interval (95% CI) 0.76 to 1.89; Austria, SMR 1.06, seven observed, 95% CI 0.43 to 2.19). A non-significant excess mortality was found for all non-malignant respiratory diseases in the French cohort due to a significant excess for pneumoconiosis (SMR 5.56, three observed, 95% CI 1.12 to 16.2). The case-control study of non-malignant respiratory disease showed an increased mortality in the highest exposure groups (odds ratio (OR) 2.5 for a cumulative exposure ≥ 800 y.mg/m³) with a significant trend (OR/100 y.mg/m³ 1.08) with cumulative exposure to talc. On the contrary, no increasing trend could be found in the case-control study of lung cancer. This result must be interpreted considering the small cohort size. Adjustment on smoking and exposure to quartz did not influence these results to any extent.

Conclusions: The mortality from non-malignant respiratory disease was found to be related to high cumulative exposure to talc dust. The small excess in lung cancer does not seem to be attributable to talc.

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Talc is mined in many countries and processed in numerous manufacturing industries for use in paints, ceramics, rubber products, roofing materials, paper, insecticides, cosmetics, and pharmaceuticals. Talc^{1,2} (Mg₃Si₄O₁₀(OH)₂) is a member of the silicates group of minerals characterised by its structure in sheets which can be separated by slight forces. This causes the plate shape of the talc particles and the smoothness in touch. Other characteristics of talc as a mineral are softness, hydrophobic behaviour, and insolubility. Given this planar structure of the talc crystal, the term talc fibres is technically not correct. However, when milled, some cleavage fragments (less than 1%) within the talc powder meet the World Health Organisation (WHO) definition of fibres, although in fact these fragments are elongated talc platelets.

As talc is formed by alteration or metamorphosis of rocks, it is associated with many types of minerals and may contain other minerals as residues, so that the mined and milled ore hardly ever consists of pure talc. Exposure to talc must therefore be considered bearing in mind the coexposures—among which quartz is the most important—specific to each site. It is noteworthy that, to our knowledge, no asbestos contamination has ever been clearly documented in the talc deposits, at least not in the European sites. Several mortality studies performed among workers from the talc industry reported inconclusive results concerning an increased risk of neoplasms of the respiratory system. Although the risk of non-malignant respiratory diseases was in excess in most of the study sites, the risk for cancer is different from study to study and may

depend on the mineralogy of the exploited mineral or other features of the cohorts.

In this paper we report the results of two historical cohort mortality studies conducted in the Austrian and the French talc industries and of two nested case-control studies focused on non-malignant and malignant respiratory diseases.

METHODS

Industrial sites and exposure assessment

The French site (site A) is in the French Pyrenees. The ore is a talc chlorite mixture which has been quarried since the end of the 19th century in an open cast pit at an altitude of 1700 m. The talc is sorted on the spot and dried and milled in a nearby talc mill. Quartz contamination is low, from non-detectable to less than 3%.

The Austrian sites comprise three mines (sites B, C, and D) with their respective mills in the Styrian Alps and a head office in the city of Graz (site E). The ore mined in site B consists of a talc-chlorite mixture with dead rock inclusions of about 25% (mainly gneiss). The dead rock is dumped in the mine so that the milled product is talc-chlorite and contains from 0.5% to 4% quartz. In site C, the material mined was a talc-dolomite aggregation with a medium talc content of 25%. The percentage of quartz in the end products was below 1%; singular parts

Abbreviations: SMR, standardised mortality ratio; ICD, international classification of diseases; JEM, job exposure matrix

in the mine, rich in dolomite, could contain 2%–3% quartz. In site D, a light greyish quartz chlorite mica schist (leucophyllite), an aggregation of more or less equal proportions of mica, chlorite, and quartz has been quarried and milled on site.

The exposure to talc dust and quartz was coded through a site specific job exposure matrix (JEM). The principles of the coding were agreed between the authors, and the codings of the JEM were harmonised before the statistical analysis. In Austria this JEM was developed by the occupational physician (HS) in collaboration with the managerial staff of the company on the basis of interviews of retired workers. In France, the JEM was developed by the occupational physician (MR) on the basis of the JEM developed for an earlier study,³ which included a more detailed assessment but did not reach as far back in time as the present one.

The talc exposure was coded in four semiquantitative categories which were based on systematic exposure measurements carried out in 1986–7 in the French site A, on less systematic measurements in 1988–92 in the Austrian sites, and on descriptions of the workplaces obtained from management and long term workers. The exposure measurements both in France and Austria were obtained with the same type of personal dust sampler worn by the worker for at least half a shift. The results are gravimetric determinations of the respirable dust fraction (for details see Wild *et al*³). The assignment of the workplaces to the four semiquantitative levels was done as follows.

- No exposure to talc was coded for office workers. A mean dust concentration of 0.2 mg/m³ based on 168 measurements was obtained in 1986 in site A for office workers. No exposure to talc occurred for those working in sites not exposed to talc. This was the case in the French mill, which included a separate power station and a carpentry, and in the mill in site D, in which no talc was milled before 1970, which does not mean that there was no exposure to dust, but that this dust did not contain any talc.

- An exposure lower than 5 mg/m³ was assessed for subjects with no direct contact to talc dust. This occurred for certain off site maintenance workers or garage mechanics, and for production workers in recent times with up to date dust confinement or local exhaust ventilation. Eight jobs were in this category in the French site in 1986, mean exposures ranged from 0.5 to 2.6 mg/m³, the range of the 100 exposure measurements carried out that year was 0.11–17 mg/m³. In Austria most production workers had belonged to this category since 1980. The 173 exposure measurements in site B between 1988 and 1992 ranged from 0.02 to 4.61 mg/m³. In site C, 33 measurements in 1991–2 ranged from 0.02 to 4.1 mg/m³.

- An exposure higher than 30 mg/m³ was assessed for past production jobs, for which a high dust exposure was documented, for instance by low visibility due to the dustiness of the workplace. In the French mill, these jobs included the milling itself, the bagging, the storing, carrying, and cleaning of jute talc bags and the sawing of so called talc pencils. The last time such an exposure was coded was for a cleaning job before 1985. In Austria this exposure level was coded for all workers in sites B and C before 1960 and for millers and onsite maintenance workers in site D between 1970 and 1980. At the end of the 1980s, no highly exposed workers remained, so that no direct exposure measurement could be obtained. However, in some extreme exposure situations which were rare in the 1980s, exposure was measured at concentrations above 50 mg/m³. Such measurements were described as quite common in the job periods attributed to the highest category. Three measurements of the exposure in such situations were identified in Austria (from the workers wearing individual protective equipment) to be 73, 82, and 159 mg/m³.

- A medium exposure between 5 and 30 mg/m³ was coded for all jobs which did not enter the preceding categories. This included the more recent French production workers in the

dustier areas such as bagging or milling, the onsite maintenance workers, or in the early days some workers in jobs near very dusty areas such as the oven workers. In Austria, this concentration was attributed to all workers in site B between 1960 and 1980 and for workers in site D from 1980 to 1990. Eleven workplaces in this category could be characterised by actual measurements in the French site A with measured mean exposures from 3.6 to 25.6 mg/m³. The range of the 193 exposure measurements was 0.21 to 134 mg/m³. In Austria 17 measurements were made in site B and eight in site C ranging between 6.5 and 19.6 mg/m³.

The main other exposure that was assessed was quartz, which occurred mostly in underground mining, tunnelling, and barrage building but also while milling minerals that contained quartz as in site D. More precisely subjects were said to be exposed to quartz if they were employed in mining or milling of leucophyllite (Austrian site D), if they were underground miners in site B before the introduction in 1960 of modern drilling techniques, or if their earlier jobs involved underground mining in sites with known exposure to quartz, or tunnelling or barrage building in the Pyrenees.

Cohort definition and data collection

The French cohort

The French cohort consisted of all male workers in site A having been employed continuously for at least 1 year between 1 January 1945 and 31 December 1994. It comprised all staff of the milling site (including administrative workers and executives). Most of the subjects employed at the quarry were excluded, because (due to the high altitude) the quarry runs only during summer. A few workers were employed in the winter also and were thus included in the cohort. The data were abstracted from several administrative records and were checked for completeness with the annual pay sheets, which were available since 1945. This cohort was followed up for mortality between 1 January 1945 and 31 December 1996. The vital status of all subjects was assessed by contacting the registry offices of the respective birth places and by searching a computerised data base of all people who had died in France since 1978. An individual tracing procedure was set up for all foreign born subjects. The cause of death was determined by matching the files of the deceased subjects with the national files of causes of death, which exist since 1968 (coded using the eighth revision of the international classification of diseases (ICD-8)⁴ until 1978 and ICD-9⁵ thereafter). For all subjects who died before 1968, we relied on the causes of death obtained from an earlier mortality study.⁶

The Austrian cohort

The Austrian cohort consisted of all male workers employed continuously for at least 1 year between 1 January 1972 and 31 December 1995, in one of the four study sites located in the federal state of Styria (Austria). The reason for starting the Austrian cohort in 1972 is that the regional mortality data are only available in a computerised form since that year. We used two sources of information for the subjects' private and employment data: the company's registries and the catalogues of the regional social insurance fund (VADOeB). Complete work histories within the company were available. The vital status of all subjects and, if no longer alive, the dates and causes of death within the study period were assessed by matching the subjects' names and their dates of birth with the national mortality data set from *Statistics Austria* (coded with ICD-8⁴ until 1979 and ICD-9⁵ thereafter).

The case-control study

Following Breslow and Day,⁷ we considered the nested case-control study as a Cox model with time variable age in which the controls are sampled from the risk set. With this approach, the risk set of a given case consisted of all subjects

Table 1 Observed (Obs) and expected (Exp) numbers of deaths, standardised mortality ratios (SMRs) (95% CI) of the main causes of death by cohort

Cause of death†	French cohort*				Austrian cohort			
	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes	294	317.5	0.93	0.82 to 1.04	67	89.4	0.75	0.58 to 0.95
Cardiovascular system	106	113.7	0.93	0.76 to 1.13	20	32.9	0.61	0.37 to 0.94
Non-malignant respiratory diseases	26	24.6	1.06	0.69 to 1.55	1	3.7	0.27	0.01 to 1.52
Pneumoconiosis	3	0.5	5.56	1.12 to 16.2	0	0.1	—	—
Digestive tract	14	17.1	0.82	0.45 to 1.38	9	8.7	1.04	0.48 to 1.97
All cancers	80	78.4	1.02	0.81 to 1.27	17	23.4	0.73	0.42 to 1.17
Stomach cancer	5	4.3	1.18	0.38 to 2.75	1	2.5	0.40	0.01 to 2.25
Mesothelioma	0	0.3	—	—	0	0.1	—	—
Lung cancer	21	17.0	1.23	0.76 to 1.89	7	6.6	1.06	0.43 to 2.19
Violent death	22	26.1	0.84	0.53 to 1.28	15	13.1	1.14	0.64 to 1.88

*In the 1968–96 period by comparison with local rates; †coded according to the ICD-8 and ICD-9.

at risk (alive and under observation) at the age at which the case has died. By this definition, another case is a potential control if he died at an older age. To account for the period effect only subjects who attained this age within the same 5 year period were considered eligible. We sampled three controls within each risk set thus achieving matched age and stratification on calendar periods.⁸ We used the STATA software and the procedure “sttocc” to implement these steps.

Two different case-control studies were thus set up.

- The lung cancer case-control study which included all cases with ICD codes 162.0 to 162.9 for their main or associate causes of death in either the 8th or the 9th revision.

- The study of non-malignant respiratory diseases included all deaths with ICD-8 codes 10.9 (silicotuberculosis) or 460.0 to 519.9 or ICD-9 codes 460.0 to 519.9 for their main or associated causes of death.

In Austria, the work histories could be abstracted from company records and were classified according to the exposure by one of us (HS) who worked as an occupational physician for the company. The smoking information was obtained from earlier unpublished studies on mortality and pneumoconiosis, from colleagues, and from records of the compensation claim insurance (AUVA).

In France, the occupational histories and the smoking information were collected by an external interviewer blind to the case-control status on the basis of existing documents or when the information was missing, by contacting former colleagues. The existing documents consisted mostly of the paper files from the previous mortality study carried out in the beginning of the 1980s,^{6,10} and the files of the occupational physician of the company.

Analytical methods

Cohort study

We compared the mortality rate of the cohort with local death rates by standard life table methods.⁷ For the French cohort the local (département de l'Ariège) and the national mortality rates were used. The local mortality rates were only available since 1968. For the Austrian cohort we used the mortality rates of the federal state of Styria. We accumulated person-years at risk for each member of the respective cohort, starting with the first anniversary after entering employment, or 1 January 1945 (Austria: 1 January 1973). In France all subjects were followed up until 31 December 1996 or earlier in the case of death. Subjects lost to follow up (3%) were censored at the day they left the company. In Austria all subjects were followed up until 31 December 1995 or earlier in the case of death. Standardised mortality ratios (SMRs) were obtained by dividing the observed number of deaths by (age and period standardised) expected numbers. Furthermore 95% confidence intervals (95% CIs) were calculated with the Poisson assumption.⁷

Case-control studies

The work histories were combined with the job exposure matrix to obtain individual estimates of cumulative exposures. Assigning concentrations of 2.5 mg/m³ for jobs with low exposure, 10 mg/m³ for medium exposure, and 40 mg/m³ for high exposure, the cumulative exposure was obtained by summing all job periods, the product of the duration of exposure by the assigned concentrations. This was done until death for the cases, and for the controls until the age at which the corresponding case died. To account for the latency period of lung cancer a second lagged estimate of the cumulative exposure was obtained by summing the exposure until 10 years before the age at death of the case.

The statistical analysis was done by conditional logistic regression¹¹ which takes into account the matching structure. This was especially important because for two cases, less than three controls were available in the risk set so that an unequal number of controls were sampled by case. Moreover, missing confounder information (especially smoking) also gave unequal numbers of controls per case, when adjusting for them.

As the main question was the cumulative effect of talc dust, this variable was fitted as a continuous variable. To avoid unnecessary small odds ratios, the cumulative exposure to talc dust was transformed into units of 100 years.mg/m³. One unit is for instance obtained as 40 years at 2.5 mg/m³ (low exposure), as 10 years of medium exposure, or as 2.5 years in a highly exposed job. Other indices characterising the exposure to talc such as the maximal talc exposure or the duration of exposure and employment were also fitted.

Smoking, exposure to quartz, or a history of underground work were fitted as binary exposed versus non-exposed variables to adjust for these variables when estimating the effect of exposure to talc.

The goodness of fit of the successive models was assessed by the likelihood ratio test.¹¹ No attempt was made to adapt the shape of the exposure-response curve to obtain a better fit given the sparseness of the data.

RESULTS

Cohort study

The French cohort comprised 1070 people, among which 712 subjects contributed person-years to the cohort before 1968 (101 deaths, 24 lost to follow up, 24 missing causes of death, 9596 person-years) and 945 subjects contributed person-years to the cohort from 1968 on (294 deaths, six lost to follow up, five missing causes of death, 19 253 person-years). From the 294 deaths, 268 (91%) were matched with the file of death certificates, 21 were obtained from the doctor, and five remained missing. In the Austrian cohort a total of 542 men was included, among them 457 still alive and 67 dead at the end of the study period, resulting in 9469 person-years.

Table 2 Data (n (%)) description of the non-malignant respiratory diseases case-control study

		France		Austria	
		Cases	Controls	Cases	Controls
Administrative information:					
Started employment	<1930	15 (38)	29 (25)	—	—
	1930–1949	16 (41)	46 (40)	1 (100)	2 (67)
	≥1950	8 (21)	41 (35)	—	1 (33)
Smoking information:					
	Missing information	3 (8)	22 (19)	1 (100)	3 (100)
Data source*	Previous documents	23 (64)	53 (55)	—	—
	Colleagues	13 (36)	43 (45)	—	—
Classification*†	Non-smoker	16 (44)	40 (43)	—	—
	Light smoker	6 (17)	16 (17)	—	—
	Heavy smoker	14 (39)	24 (26)	—	—
	Smoker‡	—	14 (15)	—	—
Occupational exposure:					
	Missing job history		4 (3)	—	—
Data source	Previous documents	37 (95)	99 (85)	1 (100)	3 (100)
	Colleagues	2 (5)	13 (11)	—	—
Employed as	Manual worker	37 (95)	100 (89)	1 (100)	2 (66)
	Office worker	2 (5)	8 (7)	—	1 (33)
	Manager	—	4 (4)	—	—
Talc exposure	None	6 (15)	26 (22)	—	1 (33)
	Light	—	12 (10)	—	—
	Medium	6 (15)	22 (19)	—	1 (33)
	Heavy	27 (69)	56 (48)	1 (100)	1 (33)
Other exposures	Quartz‡	1 (3)	2 (2)	1 (100)	1 (33)
	Underground work§	3 (8)	7 (6)	1 (100)	1 (33)
Total		39	116	1	3

*Percentage among subjects with known smoking habits; †as defined in the text; ‡smoker without further information; §in France subjects with a history of underground mining in other mines (two cases and five controls), or tunnelling (one case and two controls), in Austria underground talc mining (the case and the control are from site B).

In the early French cohort (before 1968), the SMR from all causes was 0.78 with respect to the population of France, and four deaths from non-malignant respiratory disease were observed compared with 7.16 expected. For lung cancer, one death was observed versus 3.66 expected. These figures must be interpreted with some caution as the French mortality rates exceed the local rates as both are available (by 30% for lung cancer) and 24% of the causes of death are missing. Table 1 shows the mortality from the main causes in the recent French cohort and the Austrian cohort. The lower than expected mortality in both cohorts for mortality from all causes and from cardiovascular diseases hints at a healthy worker effect. The slight excess in the mortality from non-malignant respiratory disease in the French cohort can be caused by a significant excess for pneumoconiosis based on

three cases. Mortality from non-malignant respiratory disease is, however, lower than expected in the Austrian cohort. No pleural mesothelioma was found in either cohort but the expected number is small. Mortality from lung cancer showed a slight non-significant excess in both cohorts.

Nested case-control study for non-malignant respiratory diseases

Among the subjects who died of non-malignant respiratory disease, there were 10 cases of pneumoconiosis (including silicotuberculosis) and 10 chronic obstructive pulmonary diseases (restricted to chronic bronchitis and chronic obstruction). The 20 other causes included cases of pneumonia or bronchopneumonia (five cases) and other diseases (six cases). For nine out of the 40 subjects, the cause was associated (secondary) with the main cause. It is to be noted that 39 out of 40

Table 3 Cumulative exposure (y.mg/m³) to talc in the non-malignant respiratory diseases case-control study

	Non-exposed	<100	100–400	400–800	≥800
Controls	23	19	32	19	22
Cases	6	1	8	9	16
OR		0.22	1.00	1.97	2.53
Cumulative exposure to talc (OR/100 y.mg/m ³ , 40 cases and 115 controls):					
			OR	95% CI	
All cases			1.08	1.02 to 1.16	
Pneumoconiosis			1.17	0.99 to 1.38	
COPD			1.02	0.86 to 1.20	

Table 4 Data (n (%)) description of the lung cancer case-control study

		France		Austria	
		Cases	Controls	Cases	Controls
Administrative information:					
Year of hire	<1940	5 (22)	21 (31)	—	—
	1940–1959	12 (52)	30 (45)	2 (29)	8 (14)
	≥1960	6 (26)	16 (24)	5 (71)	13 (62)
Information on smoking:					
	Missing information	11 (48)	17 (25)	—	—
Data source*	Previous documents	9 (75)	33 (66)	5 (71)	8 (38)
	Colleagues	3 (25)	17 (34)	2 (29)	13 (62)
Classification*†	Non-smoker	1 (8)	22 (44)	—	12 (57)
	Light smoker	2 (17)	5 (10)	2 (29)	3 (14)
	Heavy smoker	8 (67)	16 (32)	4 (57)	1 (5)
	Smoker‡	1 (8)	7 (14)	1 (14)	5 (24)
Occupational exposure information					
	Missing job history	—	1 (1)	—	—
Data source	Previous documents	21 (91)	62 (94)	7 (100)	21 (100)
	Colleagues	2 (9)	4 (6)	—	—
Employed as	Manual worker	22 (96)	53 (80)	6 (86)	17 (81)
	Office worker	1 (4)	11 (17)	1 (14)	4 (19)
	Manager	—	2 (3)	—	—
Exposure to talc	None	6 (26)	20 (30)	3 (43)	3 (14)
	Light	3 (13)	9 (14)	—	2 (10)
	Medium	4 (17)	8 (12)	2 (29)	8 (38)
	Heavy	10 (43)	29 (44)	2 (29)	8 (38)
Other exposures	Quartz†	3 (13)	5 (8)	4 (57)	6 (29)
	Other carcinogens	—	1 (1)	1 (14)	—
	Underground work§	2 (9)	7 (11)	5 (71)	4 (19)
Total		23	67	7	21

*Percentage among subjects with known smoking habits; †as defined in the text; ‡smoker without further information; §in France subjects with a history of underground mining in other mines (two cases and four controls), or tunnelling (three controls), in Austria all underground mining (two cases and four controls in site B, one case and no control in site C, two cases and no control in site D).

subjects come from the French cohort. The single Austrian case (from site B, as were his three controls) had ICD code 504 (pneumopathy due to inhalation of other dust). For one case only two controls met the matching criteria giving a total of 119 controls. Table 2 describes the general characteristics of the case-control study. The information about occupational exposure (list of successively held jobs) had to be obtained by interviewing colleagues for two cases and 13 controls. These numbers are respectively 13 and 43 when considering the smoking information. It is noticeable that the smoking distribution is very similar between cases and controls. The cases were employed earlier than controls, despite the matching on age, and the proportion of subjects ever exposed to a highly exposed job is higher among cases (69%) than among controls (50%). In table 3, the cumulative exposure groups showed an increasing trend, with an excess above 400 years.mg/m³. The statistical modelling of this trend as a continuous linear independent factor without any covariate adjustment gives a significant regression coefficient. Restricted to the cases from pneumoconiosis and their controls, this trend was clearly higher with an estimated slope equal to 1.17 (ν 1.08 for all non-malignant respiratory diseases). On the other hand, this trend was barely noticeable (slope 1.02) in the subfile of chronic obstructive diseases. Adjustment on potential confounders did not change this trend to any extent. The OR for quartz (based on two exposed cases and three exposed controls) was equal to 2.4, the OR for smoking was 0.71. No non-smoking subjects exposed to quartz existed in the file so that the simultaneous effect of quartz and smoking could not be estimated. The trend with exposure was found to be slightly

higher among smokers, but this interaction was not significant. Increasing trends in mortality were also found, although less clearly when considering duration of exposure, latency, and maximal level of exposure (data not shown).

Nested case-control study for lung cancer

Table 4 describes the general characteristics of the lung cancer case-control data by country. For one case only one control met the matching criteria. This gave 88 controls. Unfortunately, given the old age of the cohort, for nearly 50% of the French cases no smoking information could be ascertained, whereas such information could be retrieved for all cases and controls in the Austrian study. The classification by smoking is, however, as expected, with only one case out of 19 cases who did not smoke. Year of hire follows the cohort definitions with five cases and 21 controls first employed before 1940 in the French study compared with none in the Austrian study. Out of 30 cases 28 were blue collar workers compared with 70 out of 87 controls. Fourteen controls came from site B, two from site C, four from site D, and one from site E compared with three cases from site B, one from site C, two from site D, and one from site E. The analysis by cumulative exposure to talc (table 5) did not show any increasing trend. The ORs were even lower than unity in the two highest exposure categories. Adjusting for smoking, exposure to quartz, or underground work, or any two of these variables did not change this absence of trend, neither did the lagging of exposure estimate. These analyses showed the expected large OR (OR 21.3, 95% CI 2.07 to 219) with smoking and an increased, although not significantly so, OR for exposure to quartz (OR 2.19, 95% CI 0.74 to

Table 5 Cumulative exposure (y.mg/m³) to talc in the lung cancer case-control study

	Non-exposed	≤100	100–400	400–800	>800
Controls	23	18	15	21	10
Cases	9	6	7	5	3
OR		0.86	1.07	0.60	0.73
Cumulative exposure to talc (30 cases and 87 controls):					
		OR/100 y.mg/m ³		95% CI	
		0.98		0.88 to 1.10	

6.45). When adjusting both for smoking and quartz, quartz became significant. No interaction with smoking could be fitted given that only one non-smoking case was included. The results from analysis of the French cohort alone¹³ did not differ from the present results to any extent.

DISCUSSION

Few mortality studies among talc workers have been published. Although the mortality from non-malignant respiratory disease was increased in most of the cohorts, the only cancer risks in the talc industry were reported in early American studies among miners and millers: In 1974 Kleinfeld *et al*¹³ reported about a proportional mortality study that included 260 workers from New York State. Out of 108 deaths, 27% were due to pneumoconiosis, and there was one case of peritoneal mesothelioma. An excess in risk of lung cancer was noted: the 13 cases of lung cancer constituted 12% of all deaths compared with an expected 3.7% based on 1955 United States rates. Risk did not show any association with duration of employment. Reviews of this study^{7 14} came to the conclusion that due to lack of information on smoking or on cumulative exposure in individual workers, and due to the fact that the authors used national lung cancer rates for comparison, a firm interpretation of an increased risk of lung cancer cannot be made from this study.¹⁴ There were four successive studies conducted among miners and millers in the Gouverneur talc district of upper New York State,^{15–18} who mined and milled a natural mixture of minerals consisting of 45% tremolite, 25% serpentine, 25% talc, and 5% anthophyllite.¹⁹ Although the three first follow up studies of this population found an excess mortality from lung cancer, the last study showed that this excess was found only among workers employed for less than 1 year. The authors concluded that the lack of an exposure-response gradient in their findings is not consistent with a causal relation and that the time of occurrence of lung cancer among the talc workers is more congruent with a smoking than a talc aetiology.¹⁸ A study investigating 392 miners and millers in Vermont talc mines²⁰ (50%–90% talc, 7%–9% chlorite, and 2%–18% magnesite¹⁹) reported an increased risk of lung cancer for miners but not for millers although millers were thought to have higher exposure concentrations. The investigators mentioned several potential factors—for which no further information was available—possibly having an impact on risk (exposure to radon, smoking, previous work in another talc mine). The American Thoracic Society concluded that the results of this study did not show any risk of lung cancer related to exposure.¹⁴ Another study of a large cohort among Italian talc (47%–86% talc, 10%–40% chlorite, dolomite, and magnesite¹⁹) miners²¹ found no evidence for an excess risk of cancer. The authors attributed the increased risk of pneumoconiosis to exposure to silica. A previous study of a cohort of workers from the French site A included in our cohort,⁶ showed a significant increase in mortality for non-malignant respiratory diseases but no significant excess in cancer mortality. A study by Wergeland *et al*²² did not report any excess risk for lung

cancer in a cohort of 389 talc (55% talc, 11% chlorite, 29% magnesite¹⁹) miners and millers. Furthermore, a risk lower than unity was found for non-malignant respiratory diseases. In summary, none of the studies already mentioned was able to prove an increased risk of lung cancer among miners and millers, reliably attributable to exposure to talc, whereas the risk for non-malignant respiratory diseases was in excess in most of the study sites. There are also reports of studies of talc exposure other than in the mining industry. In 1987, a study on talc exposure in the manufacture of ceramic plumbing fixtures was published.²³ The authors found a significantly increased risk for lung cancer that showed a trend with duration of employment in “non-fibrous talc” jobs. There was no increased risk for lung cancer either among non-talc workers nor among “fibrous talc” workers. A recent study among workers in the rubber industry²⁴ suggested that the increased mortality found from lung and stomach cancer was associated with exposure to asbestos and talc dust, which were raw materials used in this industry.

None of the preceding studies attempted to investigate dose-response relations and few gave any quantitative level of exposure. Our study is a first attempt to measure the risk associated with exposures to different concentrations of talc dust, while adjusting for possible confounders. This would increase the relatively small statistical power in detecting a dose-response relation, which is an essential part of a discussion of causality.

The strength of the conclusions to be drawn from such a study depends however, apart from the statistical power, on the validity of the information collected. The different aspects to be discussed are cohort selection, causes of death, exposure assessment, and confounder information.

In our study we included by design only those employees who had worked for the company for at least 1 year continuously. This mainly had the effect of excluding the seasonal workers in the French cohort. This population was excluded for several reasons. Firstly, this population consists mostly of foreigners (Spain, north Africa) who did not live in France during the winter season and whose mortality would have been comparable neither with the local population nor the population of millers. Secondly, the mortality of this population would have been nearly impossible to trace and the causes of death would have been difficult to obtain. Thirdly, from a more fundamental point of view, the mortality of short term workers is always difficult to interpret²⁵ as the non-occupational characteristics including personal lifestyle are usually different from long term workers and can confound a dose-response relation. An already mentioned example is the study by Gamble¹⁸ who showed that the risk of lung cancer was increased only in short term workers, which he attributed to smoking and other influencing factors rather than to exposure to talc. The causes of death were mostly based on death certificates, which are probably more reliable in Austria given the high rate of postmortem examinations in this country.²⁶ Misclassification occurred certainly within the group of non-malignant respiratory disease, and some deaths from non-malignant respiratory disease and even lung cancer may have been misclassified. Moreover, no cause of death could be found for 24 deaths in the early French cohort. This may have biased the SMR although the same misclassification occurred in the population rates. However, it is unlikely that diagnosed lung cancers or non-malignant respiratory disease were in fact other causes. Therefore if some cases were not diagnosed, the risk set sampling paradigm ensures that this results in a loss of statistical power but not in bias. This conclusion relies on the assumption that the not-diagnosed cases had similar exposure to the diagnosed cases.

The validity of the exposure assessment as we implemented it, depends on the one hand on the preciseness of the job histories and on the other hand on the industry specific JEM. Although the job histories from the Austrian data can reasonably be relied on as individual job histories were kept in the

company files, the French data are more questionable as they relied mostly on data from former studies in the early 1980s.⁶⁻¹⁰ The individual work histories recorded in 1980 relied even at that time on rather ancient memories. The French work histories only rarely recorded more than one job and when several jobs were mentioned, no time scale could be assessed. However, the possible misclassifications should not result in large quantitative misclassifications. The same (high) exposure level was attributed to nearly all earlier production workers by the JEM, only some specific jobs such as maintenance workers were assigned medium exposures and some offsite jobs (cook or work at the power station) were considered to be non-exposed. The likelihood of misclassification between these broad categories is therefore low. The JEM has been kept deliberately coarse with only four categories which span considerably different exposures. The concentrations assigned are to a certain extent arbitrary as only the two lower exposure levels could be calibrated by actual exposure measurements. The concentrations chosen (2.5 mg/m³ for light exposure and 10 mg/m³ for medium exposure) were higher than the mean of the exposure measurements, but it was thought that even within these categories, the working conditions had already improved at the end of the 1980s when the measurements were taken. The most arbitrary concentration is, however, the 40 mg/m³ assigned to the high exposure category, which only relied on some measurements made in high exposure circumstances which still happened occasionally in the 1980s. However, given that such circumstances were the rule rather than the exception in earlier times, the mean exposure in these highly exposed jobs was certainly above 30 mg/m³. On the other hand, it probably did not exceed 60 mg/m³ except in some very specific tasks such as cleaning jute bags of milled talc. It is none the less safer to interpret a value of 400 years.mg/m³ as 40 years of the present standard of high exposure or 10 years of extreme exposure. A retrospective validation of the exposure assessment is that it enabled the detection of a dose-response relation for mortality from non-malignant respiratory diseases despite a mortality that was only slightly above the expected.

The last possible validity issue refers to the confounder information which is mainly smoking in this study and is discussed with its effect on the results of the case-control studies.

As already stated, the clearest result of this study was the significant dose-response relation between cumulative exposure to talc and mortality from non-malignant respiratory diseases. This dose-response relation is due to the large odds ratios in the categories above 400 years.mg/m³. However, given the uncertainty in the exposure assessment and the relative small data set, this value can hardly be interpreted as a threshold under which no risk exists. It is to be noted that this dose-response relation is high for the study of pneumoconiosis but virtually undetectable in the analysis restricted to chronic obstructive pulmonary disease. This may indicate that high exposure to talc dust is fibrogenic²⁷ but does not cause obstructive syndromes. This agrees also with findings in Wild *et al*³ in which a restrictive syndrome rather than an obstructive syndrome was found. It is not clear however whether this effect is specific to talc. An alternative explanation has been forwarded: a hypothesis coined as "particle overload",²⁸ states that the pulmonary clearance by the alveolar macrophages is inhibited by high exposure to highly insoluble, but non-cytotoxic, particles. Oberdörster concluded from an experimental 2 year inhalation study²⁹ that "talc particles behave like other low-toxicity particles such as TiO₂ or toner with respect to lung clearance and chronic pulmonary inflammation".

A somewhat surprising result of the analysis is the low risk of smoking. It might be that subjects with chronic respiratory problems stop smoking earlier or do not take up smoking at all. This hypothesis is all the more plausible as information on smoking has often been obtained from relatives or colleagues

and some former smokers might be misclassified as non-smokers. However when restricting the analysis to chronic obstructive pulmonary disease, the expected risk from smoking was OR=2.1. The risk from smoking was also found in the lung cancer study. It is therefore unlikely that the low smoking OR is due to a major misclassification in the data collection for smoking.

The analyses of the case-control studies on lung cancer did not find any dose-response relation, be it by maximal dose, latency, duration of exposure, or cumulative exposure. This fact, as well as the lower risk in exposed than in non-exposed blue collar workers, indicates that the slight excess found in the cohort study is unlikely to be due to the exposure to talc. It is also unlikely that this finding is due to exposure misclassification, as already discussed. However, this negative finding must be interpreted in the context of the relatively low power of this study. A formal evaluation of the power is not feasible as our analysis relied mostly on an internal estimation of a dose-response relation. However, despite all the uncertainties surrounding the trend estimate, the upper confidence level of this estimate indicates the approximate levels of risks excluded by our study. Thus a risk of lung cancer higher than 1.10/100 years.mg/m³ is unlikely. It must be further stressed that this result is obtained in a cohort followed up over 50 years with considerable exposure and with a mean duration of employment exceeding 20 years, in which a not too obvious trend for non-malignant respiratory diseases could be shown.

There might be some residual confounding due to exposure to quartz especially in the Austrian site D as this exposure could not be measured. Given that this site contributed only two cases, this should not be a major confounder. Moreover restricting the analysis to the subfile of sites A and B, for which the exposure was qualitatively close, did not change the results. In the subfile with known smoking habits the adjusted and non-adjusted ORs were similar, which hints at an absence of confounding, but does of course not indicate whether the smoking distribution is similar among subjects with or without the smoking information. The missing smoking information in nearly a third of the cases remains the main weakness of this study on lung cancer.

CONCLUSIONS

For highly exposed subjects, the mortality from non-malignant respiratory diseases seems to increase with cumulative exposure to talc. This contrasts with the absence of any dose-response relation for lung cancer.

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